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Modelling efforts needed to advance herpes simplex virus (HSV) vaccine development: Key findings from the World Health Organization Consultation on HSV Vaccine Impact Modelling

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Abstract

Development of a vaccine against herpes simplex virus (HSV) is an important goal for global sexual and reproductive health. In order to more precisely define the health and economic burden of HSV infection and the theoretical impact and cost-effectiveness of an HSV vaccine, in 2015 the World Health Organization convened an expert consultation meeting on HSV vaccine impact modelling. The experts reviewed existing model-based estimates and dynamic models of HSV infection to outline critical future modelling needs to inform development of a comprehensive business case and preferred product characteristics for an HSV vaccine. This article summarizes key findings and discussions from the meeting on modelling needs related to HSV burden, costs, and vaccine impact, essential data needs to carry out those models, and important model components and parameters.

Introduction

In 2014, the World Health Organization (WHO), the National Institutes of Allergy and Infectious Diseases (NIAID), and global technical partners outlined a comprehensive roadmap for the development of effective new vaccines against sexually transmitted infections (STIs).¹ The roadmap highlighted the urgent need for a vaccine against herpes simplex virus type 2 (HSV-2), because of the large numbers of HSV-2 infections globally, with more than 400 million infections estimated in 2012,² the fact that HSV-2 fuels the HIV epidemic by increasing the risk of HIV acquisition and transmission several-fold,³ and the limited population impact of current HSV prevention measures.⁴ An HSV vaccine could have an impact not only on suffering due to genital ulcer disease (GUD), of which HSV-2 is the most common cause worldwide,⁵ but also on neonatal herpes, an uncommon but devastating condition, and potentially on the spread of HIV infection. Such a vaccine might also protect against HSV type 1 (HSV-1), which typically causes orolabial infection but has been increasingly implicated as a cause of genital herpes.^{6,7}

WHO and global partners are undertaking several activities to advance the global roadmap for STI vaccine development, and in particular, the critical need for an HSV vaccine.⁸ Preparations are underway to develop a global business case for HSV vaccines, to clearly articulate the public health need, global market, and anticipated pathway and costs for developing, licensing, and implementing an HSV vaccine, as well as the predicted cost-effectiveness and return on investment. The business case, sometimes referred to as the value proposition, is intended to support strategic planning and catalyse engagement and investment in HSV vaccine development, not only from innovators, vaccine manufacturers, and funders, but also from regulators, national decision-makers, and other key stakeholders across the public health spectrum. A complementary roadmap activity is generation of preferred product characteristics (PPCs) for HSV vaccines. PPCs reflect a formal WHO process to define and reach consensus on the desired characteristics of vaccines that would address priority public health and programmatic needs, particularly for low- and middle-income countries (LMICs).⁹ PPCs are intended to provide early guidance to product developers and policy makers to ensure that vaccine candidates will not only meet requirements for licensure, but more importantly that they will benefit LMICs and can be rapidly implemented following approval.

Mathematical modelling can inform several critical areas of the business case for HSV vaccine and PPC development (Figure 1). The first step in generating a business case is to build a comprehensive picture of the public health burden of HSV infection, including the economic burden. Model-based estimates of the global and regional burden of HSV disease and its costs to society are necessary since global surveillance for these outcomes does not exist.² The next step is to model the

theoretical population-level impact of an HSV vaccine on the disease and cost burden, in the context of other available inventions (e.g., anti-viral therapy). These models incorporate assumptions that are defined within PPCs, such as efficacy requirements, target population, and duration of protection. In turn, modelling can help clarify the range of vaccine characteristics that can maximize the vaccine's public health impact and cost-effectiveness,¹⁰ to refine the ideal attributes defining PPCs and the target product profile used by vaccine developers (Fig 1). Target product profiles incorporate similar characteristics as the PPCs but may differ in that they typically also consider high-income country (HIC) markets. Once the product profile is established, the vaccine development and licensing pathway, its associated risks and costs, and predicted revenue are considered in building a robust case for investment.

In March 2015, WHO convened a two-day meeting of experts in HSV modelling, epidemiology, and health economics to outline critical modelling efforts needed to inform development of an HSV vaccine business case and PPCs: the WHO Consultation on HSV Vaccine Impact Modelling. The objectives of the meeting were 1) to review existing models and identify modelling needs related to: a) HSV infection and disease burden at global and regional levels, b) the costs of HSV infection and its sequelae, and c) the theoretical impact of an HSV vaccine; and 2) to outline key modelling activities to address the gaps, including prioritization of needed models on HSV burden, costs, and vaccine impact, determination of essential data needs to carry out those models, and guidance on important model components and parameters. This paper summarizes the main findings and discussions from the meeting.

HSV natural history and vaccine development efforts

HSV-1 and HSV-2 cause lifelong, incurable infections. After infecting skin or mucosa in the oral (HSV-1) or genital (HSV-1 or HSV-2) area, HSV establishes persistent infection in neural ganglia. HSV can then intermittently travel back down nerve axons to cause either symptomatic genital or oral ulcers (often called a "recurrence") or asymptomatic viral shedding.⁵ This process can occur repeatedly and frequently over a person's lifespan. The majority of HSV infections are unrecognized or asymptomatic. Asymptomatic viral shedding occurs frequently, and most HSV transmission occurs in the absence of symptoms.¹¹

HSV-2 infection, which is sexually transmitted, is the leading cause of GUD globally. Regardless of whether an HSV-2 infection is symptomatic or asymptomatic, evidence suggests that it increases the risk of acquiring HIV infection by approximately 3-fold³ and can be transmitted to a neonate to cause neonatal herpes. Although neonatal herpes is rare, occurring in approximately 1 in 3000 to 1 in

12,000 live births,¹²⁻¹⁴ about 60% of infections are fatal if left untreated, and surviving infants may have long-term disabilities.¹⁵ HSV-2 is the most common cause of recurrent meningoencephalitis, and can also cause severe hepatitis and disseminated infection in immunocompromised people.⁵

HSV-1 and HSV-2 share >80% genetic homology of their protein-coding regions but have different clinical and epidemiologic features.¹⁶ HSV-1 typically causes orolabial infection, with clinical manifestations ranging from herpes labialis (“cold sores”) to gingivostomatitis and pharyngitis. Less common complications include sporadic encephalitis and keratitis.¹⁷ However, HSV-1 is now the leading cause of symptomatic first-episode genital herpes in some HIC settings, where infection in childhood has been decreasing.⁷ Genital HSV-1 infection has a milder natural history and is less likely to recur than HSV-2 infection.¹⁸ The virus types also have complex immunological interactions. For example, although HSV-1 infection does not appear to prevent acquisition of HSV-2, it does reduce the likelihood that acquired HSV-2 infection will be symptomatic.¹⁹

Antiviral therapies for genital HSV infection can reduce the number of days with symptoms during recurrences and can be taken daily to reduce the frequency of recurrences. Within discordant relationships, use of antiviral therapy by the HSV-2 seropositive partner can decrease transmission by up to 50%.²⁰ Condom use also partially decreases both HSV-2 acquisition and transmission.²¹ However, neither of these approaches is used extensively enough to limit incidence or prevalence at the population level, and vaccines are likely the best option for effective HSV control.

No licensed HSV vaccines currently exist, but a number of vaccine candidates are in various stages of preclinical and clinical development.²² These vaccines are primarily designed to prevent acquisition of HSV-2 infection before exposure (prophylactic) and/or to reduce symptoms and viral shedding among those with existing genital HSV-2 infection (therapeutic). The most advanced candidates to date have been recombinant glycoprotein subunit prophylactic vaccines, which have been studied in clinical trials in more than 20,000 people.^{6,23,24} In a trial in the late 1990s, an HSV glycoprotein D-2 (gD2) vaccine reduced HSV-2 infection (by 40%) and disease (by 70%) among HSV-1 seronegative women, but not among men or HSV-1 seropositive women.²⁴ However, in a follow-up trial among over 8000 HSV-1/HSV-2 seronegative women, the gD2 vaccine failed to prevent HSV-2 infection or disease.⁶ Interestingly, the vaccine did result in a significant decrease in HSV-1 infection (35% efficacy) and HSV-1-related genital disease (58% efficacy).

In recent years, considerable focus has been placed on development of therapeutic vaccines.²² A recent Phase II trial showed a 65% decrease in both genital HSV-2 shedding frequency and days with genital lesions after the therapeutic vaccine series.²⁵ All previous HSV vaccine trials, for both

prophylactic and therapeutic vaccines, have been conducted in HICs. A prophylactic vaccine is most needed in LMIC settings such as sub-Saharan Africa, where the prevalence and incidence of both HSV-2 and HIV are highest and where HSV-2 is thought to increase the risk of HIV infection, even in the absence of symptoms.^{2,3} The effect of a therapeutic vaccine on the risk of HIV acquisition among HSV-2-infected people remains unknown and could vary according to its immunologic mechanism and whether it may increase or decrease the presence of activated CD4+ T cells in the genital tract that are targets for HIV infection.²⁶

Model-based estimates of the burden of HSV infection and sequelae

Meeting participants reviewed existing estimates of HSV infection and disease burden and identified critical gaps, needs and considerations. Key findings are summarized in Table 1. WHO estimated that 417 million people aged 15–49 years had HSV-2 infection globally in 2012.² The Global Burden of Disease (GBD) Study 2013 estimates were higher at over 1 billion HSV-2 infections worldwide, primarily because all ages were considered.²⁷ Data used in both estimates were sparse in some regions. However, meeting participants generally agreed that current estimates were sufficient to inform the business case, but suggested comparison of WHO and GBD models, incorporation of data from high-risk populations, and exploration of additional data sources. The first global and regional estimates of HSV-1 infection were finalized after the meeting, estimating that 1.7 billion people aged 0–49 years have HSV-1 infection and 140–280 million 15–49 year-olds have genital HSV-1 infection.²⁸ Prevalence estimates used to generate these projections were even sparser than for HSV-2, and meeting participants recommended evaluation of newer HSV-1 serological data where feasible and better data on the proportion of HSV-1 infections that are genital, especially in LMICs.

Meeting participants identified more gaps related to HSV disease outcomes, such as GUD, neonatal herpes, and HSV-associated HIV infection. No detailed models estimating HSV-related GUD were identified. Meeting participants encouraged such a model, incorporating HSV-2 and HSV-1 natural history and available GUD surveillance data. The first global estimates of neonatal herpes were published after the meeting, and estimated that roughly 14,000 cases occurred annually during 2010–2015 (10 cases per 100,000 livebirths).¹⁴ The estimates were based on HSV-1 and HSV-2 prevalence and incidence estimates, pregnancy rates by region and age, and published risks of mother-to-child transmission by HSV type and stage from the United States.¹² While these estimates are a good starting point to inform the business case, better primary data are needed on mother-to-child HSV transmission risks and neonatal herpes incidence, especially in LMICs, to reduce uncertainty and refine future estimates. Several studies have evaluated the population attributable fraction of HIV due to HSV-2 infection in different settings.^{29–31} However, meeting participants agreed

that updated models, considering the degree to which incident HIV infections are attributable to HSV-2 and incorporating newer data on the HSV-HIV interaction, would be important to understand the potential impact of an HSV vaccine on HIV incidence under different epidemiologic scenarios, as outlined in Table 1. Additional reviews of HSV-1-related oral disease and other HSV-related outcomes, such as encephalitis, keratitis, and the psychosocial impact of HSV infection, would provide a more complete picture of the burden of HSV infection and the potential benefits of an HSV vaccine.

Summary health measures such as quality-adjusted life years (QALYs), disability-adjusted life years (DALYs) and years lived with disability (YLDs) allow comparison of disease burden across multiple diseases and disease states. QALYs measure both life expectancy and the quality of remaining life-years. The relative quality of life of a health state is often called the “QALY weight” or “health utility” (between 0 and 1; 0=death, 1=perfect health), which can be assessed with a range of available tools. YLDs measure the loss of health associated with a condition using a “disability weight,” and DALYs reflect YLDs plus years of potential life lost due to premature mortality. Although QALY weight estimates for adult HSV infection are limited, several tools exist to estimate the impact of HSV on quality of life, primarily incorporating the effect of symptoms but also including stigma and impact on relationships.³² QALY estimates for neonatal herpes are relatively more abundant in existing literature.³³⁻³⁵ Future needs include clarifying how to derive QALY estimates from existing quality of life scores, and obtaining quality of life data in LMICs. The GBD study estimated that HSV-2 infection resulted in 311,600 YLDs in 2013 from GUD alone, using non-HSV-specific disability weights (e.g., “mild infection” for recurrences).²⁷ The most severe disease outcomes, neonatal herpes and HSV-associated HIV infection, were not included. Better data on these outcomes, their inclusion in YLD/DALY estimates, and improved disability weights, would considerably advance understanding of HSV burden.

Model-based estimates of the economic burden of HSV infection and sequelae

Model and data needs related to estimating the economic costs of HSV infection are summarized in Table 2. A few national estimates of the direct annual costs of diagnosing and treating HSV-2 infection, and of the lifetime cost per case, exist for the United States. For example, in 2008 the annual direct cost of HSV-2 infection was estimated to be \$541 million.³⁶ One study has also estimated indirect costs of genital herpes (e.g., productivity losses due to absenteeism from work) at \$214 million.³⁷ These conservative estimates do not include costs of neonatal herpes nor HSV-associated HIV. No such estimates have been found for other countries. Although lifetime cost-per-case estimates are limited, a wide range of itemized cost components are available for specific

procedures and conditions in HICs, e.g., costs related to HSV testing, counselling, suppressive therapy, and clinician visits.³⁸ Meeting participants agreed that models to estimate aggregate annual and lifetime costs per case of HSV infection were needed outside the U.S., especially for LMICs. In addition, cost estimates incorporating neonatal herpes and HSV-associated HIV infection costs and updated data on HSV testing, antiviral use, and other factors would be important in all settings. To do this, it will be important to get better data on HSV care and treatment costs, healthcare seeking and testing practices for HSV disease, and utilization rates of HSV therapy including over-the-counter expenses and traditional medicine therapies in the informal sector, especially for LMICs. Use of administrative and health insurance claims data, and exploration of validated healthcare costs for related conditions in LMICs, were highlighted as potential avenues for gathering new data.

No existing comprehensive cost estimates were found for HSV-1 infection, and meeting participants agreed that such estimates, incorporating current data on utilization of care and treatment for HSV-1-related outcomes in both HICs and LMICs, would be valuable. Better information on HSV-1 disease occurrence and natural history will be useful, as will a review of oral HSV treatment and administration costs as they differ from genital HSV costs, e.g., topical treatment. Evaluation of administrative or claims data on oral HSV-1 evaluations and treatment could provide important information.

Although costs of neonatal herpes and HSV-associated HIV infections have not been systematically included in aggregate cost estimates for HSV infection, estimates of the lifetime cost per case of these outcomes are available, as are itemized cost components. The estimated lifetime cost per case of neonatal herpes has been over \$90,000 in the U.S. on average, but has ranged to much higher estimates depending on how long-term disability costs were included in models.³⁸ The acute hospitalization cost per case has been estimated to be \$40,044 alone.³⁹ Several studies of the cost-effectiveness of HSV screening and suppressive therapy in pregnant women (also in the U.S.) highlight the need to consider prevention costs, including Caesarean sections, in addition to the costs of treating neonatal herpes.⁴⁰ Estimates of lifetime costs of HIV infection exist, though those costs have not been applied specifically to HSV-related HIV infection.⁴¹ In addition to inclusion of costs related to neonatal herpes and HSV-associated HIV infection, important needs include lifetime cost-per-case estimates for neonatal herpes in LMICs, and updated estimates using current data on neonatal herpes costs, clinical practice, and long-term disability as well as indirect cost estimates. Better data and estimates related to neonatal herpes incidence in LMICs and the attributable fraction of HIV due to HSV-2 infection will be critical in generating comprehensive HSV-related cost estimates.

Modelling efforts related to vaccine impact

To determine key modelling needs to predict HSV vaccine impact, meeting participants discussed critical features such models would need to inform a comprehensive business case and PPCs. Dynamic models accounting for HSV transmission allow assessment of the potential impact of a vaccine in a population beyond the direct benefits to vaccinated individuals (i.e., account for herd immunity), and allow exploration of impact across different epidemiologic contexts.^{10,42} Such models can incorporate sexual contact patterns, the biology and natural history of the infection, susceptibility, transmissibility, interactions with other infections, and availability and characteristics of competing interventions, which can all vary across populations. Meeting participants discussed that there may be some limited utility for a simple static model, which assumes straightforward reductions in the per-person, age-specific incidence rates of HSV-related outcomes according to vaccine efficacy assumptions, to provide a high-level overview of the potential magnitude of costs and benefits of an HSV vaccine.⁴³ However, it was emphasized that dynamic models are more appropriate to produce valid predictions of the theoretical impact of a vaccine in altering the natural history of the infection, interrupting HSV transmission, and reducing the population-wide incidence and prevalence of infection and disease.

Critical questions for HSV vaccine impact modelling include:

- Which *populations and geographic/epidemiologic settings* are considered?
- Which *type of vaccine, prophylactic or therapeutic*, is modelled?
- How is *HSV-1 infection* incorporated in the models?
- Which *disease outcomes* are considered in the models?
- How are *vaccine characteristics* modelled?
- What are the most critical *sensitivity and uncertainty analyses*?
- Are *cost analyses* incorporated into vaccine impact models?

In preparation for the meeting, a literature review was conducted on existing mathematical models with relevance for assessing HSV vaccine impact. Thirty articles modelling dynamic HSV transmission were reviewed, including 8 articles directly modelling HSV vaccine impact.⁴⁴⁻⁵¹ Overall, the HSV vaccine impact models predicted that even an imperfect HSV vaccine could have population benefits in terms of decreasing HSV prevalence and incidence; however, the models differed with respect to the predicted magnitude and timeframe required to achieve these benefits. A detailed summary and technical review of these models, including description of model structures, parameters and assumptions, outcomes, and how those factors affected results of the different models, can be

found in the review by Spicknall et al.⁵² The ability of existing models to inform the HSV vaccine business case and evaluate PPC parameters, as well as identification of key remaining modelling and data gaps, are discussed below in the context of the critical questions outlined above.

Populations and/or geographic/epidemiologic settings

Of the existing studies, four modelled HSV-2 vaccine impact in North America,^{46,47,50,51} two modelled impact in African settings,^{44,45} and two did not specify a setting.^{48,49} Baseline HSV-1 and HSV-2 prevalence and incidence rates, sexual behaviour and networks, HIV prevalence, and vaccine delivery and healthcare costs can vary greatly across settings and can have a substantial impact on potential vaccine effectiveness and cost-effectiveness. Meeting participants felt it important to undertake dynamic modelling studies in at least three settings based on a combination of income status and HSV/HIV epidemiology: 1) a high income, low HIV prevalence setting (e.g., US, UK); 2) a low-income, high HSV/HIV prevalence setting (e.g., a sub-Saharan African country); and 3) a middle-income, low to moderate HSV/HIV prevalence area (e.g., Brazil, China). Availability of good data on sexual behaviour, HSV and HIV prevalence and incidence, and transmission risks across subgroups will be important for all selected settings.

Prophylactic versus therapeutic vaccine

The main focus of existing modelling studies has been prophylactic vaccines; only one exclusively considered therapeutic vaccines.⁵¹ Prophylactic vaccines could also have disease-modifying effects for breakthrough infection, and this has been modelled previously.^{44-46,50} However, much of the recent research and development activity has been focused on therapeutic HSV vaccines. Meeting participants discussed the need for modelling both prophylactic and therapeutic vaccines. Considerations can differ for each, e.g., target population, with prophylactic vaccination targeted primarily before the onset of sexual debut, and therapeutic vaccination being given only to those who have recognized genital herpes infection. As such, the structure and costs of vaccine delivery differ between the vaccine types and also vary by setting. Another important consideration relates to the HSV-HIV association. Because HSV-2 infection increases the risk of HIV acquisition, even with no clinical disease, a prophylactic vaccine may be preferable in settings with high HIV prevalence. Nonetheless, reducing HSV disease and shedding episodes with a therapeutic vaccine might reduce HSV transmission in the population and reduce microscopic ulcerations that are portals of entry for HIV. However, theoretically if a vaccine induces activated CD4+ immune cells in the genital area as a mechanism of action, this might increase the number of target cells for HIV infection. Modelling analysis could vary vaccine-associated benefits and risks to explore the potential impact of a

therapeutic HSV vaccine on HIV infection. Data that can shed light on the mechanisms of action of new vaccine candidates would be extremely valuable.

HSV shedding has been a key outcome in therapeutic vaccine trials (in addition to reduction in clinical recurrences). Thus, a better understanding of the association between reduction in shedding and translation to reduction in HSV transmission as well as susceptibility to HIV acquisition, is critical. Within-host models have attempted to predict transmission thresholds for HSV shedding, estimated to be around 10^4 DNA copies, but such models are difficult to validate clinically and uncertainty remains.⁵³

HSV-1 infection

Two published HSV vaccine impact modelling studies only modelled vaccine delivery for HSV-1 seronegative women, based on early gD2 vaccine trials.^{24,46,47} Other models have not explicitly considered HSV-1 infection. Meeting participants agreed that future models need to incorporate HSV-1 infection, in several respects. HSV-1 infection may be a potential target of vaccine action, may modify vaccine efficacy against HSV-2 infection, and may have other interactions with HSV-2. Ideally an HSV vaccine would prevent both HSV types, and the most recent Phase III trial of the gD2 vaccine showed a significant vaccine effect on HSV-1 infection.⁶ Including vaccine efficacy against HSV-1 infection would broaden the range of HSV-associated outcomes that could be prevented with a vaccine and thus improve potential cost-effectiveness. It would also influence the target age at vaccination. HSV-2 vaccines have typically been designed with adolescents as the target population. However, the target group for an HSV-1 and -2 vaccine would likely be infants or children, especially in LMICs, where most people acquire HSV-1 infection prior to adolescence.²⁸ If the vaccine is efficacious against HSV-2 infection only among HSV-1 seronegative people, this also has implications for target age of vaccination and costs of vaccine delivery. Dynamic models can also incorporate effects of prior HSV-1 infection on development of HSV-2 disease.

Disease outcomes

Most of the currently published dynamic models of potential HSV vaccine impact assessed only population HSV incidence and prevalence as the main disease outcomes, although one model assessed ongoing HIV transmission.⁴⁵ Meeting participants agreed it will be important to have a comprehensive assessment of the potential impact of an HSV vaccine on the most important disease outcomes, including in particular neonatal herpes and HSV-associated HIV infections, as well as potential outcomes of HSV-1 infection. Critical to such efforts will be better data on the proportion

of HSV infections leading to these outcomes in different settings, and the associated QALYs or DALYs, as discussed above.

Vaccine characteristics

Meeting participants discussed several considerations related to how crucial vaccine characteristics are modelled. In terms of vaccine efficacy, the clinical endpoints modelled can affect predicted population outcomes: efficacy against infection, clinical disease, viral shedding, or a combination of these. Vaccine impact models can be useful in determining the most important clinical endpoints to measure in trials and how different endpoints affect efficacy outcomes. Another important consideration is how efficacy is modelled. For example, for a vaccine with presumed partial efficacy, a model can assume that only a fraction of people are fully protected (“take”-type protection) or that all people have protection against a fraction of exposures (“degree”-type protection), with varying results.⁴² Duration of protection provided by a vaccine is another key characteristic, though a firm estimate of duration requires long-term follow-up. Its impact may depend on the age at vaccination and how waning of protection is modelled. Important cost impact considerations include the number of doses and other factors affecting the cost of the vaccine and its delivery.

Sensitivity and uncertainty analyses

Sensitivity analysis involves varying key parameters in a model to determine their influence on model predictions. Uncertainty analysis involves using a range of plausible parameter values, which are identified after calibrating the model to selected epidemiological outcomes, to produce estimates that reflect the uncertainty in the input parameters. As no licensed HSV vaccine currently exists, sensitivity and uncertainty analyses can be useful to delineate the range of possible impacts for the business case and to define PPCs under different conditions, determining in which context HSV vaccines can be most and least useful. For example, what level of vaccine efficacy against infection is required to have an acceptable population impact and cost-effectiveness in different settings? Meeting participants agreed it would be important to conduct these types of threshold analyses, which can be refined and narrowed as better data become available for different parameters. In addition to varying vaccine efficacy, sensitivity and uncertainty analyses can explore the impact of varying vaccine uptake, duration of vaccine protection, vaccine costs, and other parameters.

Cost analyses

None of the published dynamic models of HSV vaccine impact include HSV disease costs, nor the relative cost-benefit of a vaccine were one available. Meeting participants agreed that in the future,

cost-effectiveness analyses will be needed to incentivize product development, alongside estimates of the costs of vaccine research and development. These analyses can also shed light on the time to return on investment for different price scenarios, and can guide strategic decision-making and policy once a vaccine becomes available. In the simplest format, costs per infection and outcome can be applied to predicted number of infections and disease outcomes averted with a vaccine.⁴³ More detailed cost-effectiveness models can incorporate the role of alternative interventions, not just for HSV treatment (e.g., suppressive therapy) but also for prevention and treatment of HSV-associated outcomes (e.g., antiretroviral therapy for HIV infection), and should include the operational costs of the vaccine and its delivery in different settings.⁴²

Conclusions

Participants in the WHO Consultation on HSV Vaccine Impact Modelling identified several critical modelling and data needs to inform development of a comprehensive business case and PPCs for an HSV vaccine. The business case will be driven by the estimated burden of HSV infection and disease and associated costs. Good global and regional estimates exist for HSV-2 and HSV-1 infection, but more work is needed in estimating disease outcomes of HSV infection. To do this, better primary data are needed on neonatal herpes incidence and mother-to-child transmission risks in LMICs, and existing models of the fraction of HIV infection attributable to HSV-2 can be updated and adapted to different settings and epidemic stages. Assessment of HSV-1 infection outcomes will help define the full scope of HSV-associated disease. Robust QALY/DALY estimates incorporating the full impact of HSV infection on health and well-being are also needed. Several cost estimates and itemized cost components are available in HICs, but similar estimates for LMICs are essential, as is inclusion of costs related to neonatal herpes and HIV infection. Better data on healthcare and treatment utilization related to HSV and its outcomes will improve cost modelling for all settings. Given wide-ranging data needs, “expected value of information” analyses can assist in strategizing about which data to collect most urgently to inform vaccine impact modelling and the business case.^{54,55} These types of modelling analyses help quantify the added value of a decision made with perfect versus imperfect information for different parameters, which can help prioritise the parameters and the studies to refine them.

In order to optimally assess the theoretical population impact of an HSV vaccine, meeting participants concluded that new dynamic modelling efforts would be valuable in varied settings according to HSV and HIV epidemiology and country-income status, for both prophylactic and therapeutic vaccines. Existing dynamic models provide a good foundation for these activities. Comparison of model results can provide insight and help reach consensus on the optimal features

of new or updated models to inform the HSV vaccine business case and PPCs.⁵² Meeting participants agreed that inclusion of HSV-1 infection in dynamic models, as both an outcome and modifier of HSV-2 infection, was crucial, as was inclusion of a broader range of disease outcomes, especially neonatal herpes and HIV infection. Sensitivity and uncertainty analyses of the vaccine characteristics modelled will be especially important in defining PPCs for HSV vaccines. Finally, meeting participants supported incorporation of cost analyses into vaccine impact models to build a coherent business case. These activities will advance efforts to develop an efficacious and cost-effective HSV vaccine, a critical goal for global public health.

Participants in the WHO HSV Vaccine Impact Modelling Meeting

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Disclosures/Conflicts of interest

Drs. Boily, Broutet, Chesson, Deal, Garnett, Giersing, Gift, Gottlieb, Hutubessy, Looker, Mogasale, Moorthy, Ndowa, Newman, Schiffer, Spicknall, Teerawattananon, Vickerman and Williams report no potential conflicts of interest. Dr. Kassebaum was a consultant at a one-day meeting funded by Merck in 2012.

Disclaimers

Drs. Gottlieb, Giersing, Moorthy, and Broutet are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions or policies of the World Health Organization.

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Table 1: Key gaps to be addressed related to modelling of HSV burden

Burden of:	Summary of existing or planned models/estimates	Major gaps/ new modelling efforts needed	Key new data needs	Important considerations
HSV-2 infection	<ul style="list-style-type: none"> Overall good global estimates; sparse data for some regions Global and regional estimates of HSV-2 infection for 2012 (WHO) Global Burden of Disease (GBD) Study 2013 estimates 	<ul style="list-style-type: none"> Comparison of differences between WHO/GBD estimates to understand underlying methods/assumptions Incorporate HSV-2 data from high-risk groups to strengthen WHO estimates, as in GBD study Update models as new/better data become available 	<ul style="list-style-type: none"> Nationally-representative surveys ideal but not realistic Explore existing but unpublished HSV-2 serologic data from HIV prevention trials, other studies 	<ul style="list-style-type: none"> Clarify methods for using high-risk data to inform general population estimates for HSV-2 Current estimates generally sufficient to inform business case
HSV-1 infection	<ul style="list-style-type: none"> First global and regional HSV-1 estimates (for 2012) published in 2015, for HSV-1 infection overall and HSV-1 genital infection Data sparse, and more limited overall than for HSV-2 	<ul style="list-style-type: none"> Update models as new/better data become available 	<ul style="list-style-type: none"> New serological data to inform estimates, especially in certain LMICs would be valuable Better data on the proportion of new HSV-1 infections that are genital, including outside the US Better understanding of local immunity and interaction between HSV types with genital HSV-1 	<ul style="list-style-type: none"> Current estimates generally sufficient to inform business case
Genital ulcer disease	<ul style="list-style-type: none"> No identified comprehensive modelled estimates Rough estimate obtained by applying simple proportion ever symptomatic to global HSV-2 numbers 	<ul style="list-style-type: none"> Model of global and regional HSV-related GUD needed Incorporate both HSV-2 and HSV-1 and natural history Triangulate from 2 scenarios: working forward from global HSV infection estimates, and backward from surveillance of GUD and proportion HSV-related in different settings 	<ul style="list-style-type: none"> Analysis of data from DHS surveys: 75 countries doing GUD surveillance Systematic review of etiologies of GUD in different settings New studies of GUD etiology studies and proportion seeking care for GUD Better data on natural history of genital HSV-1 Better data on proportion of genital HSV with symptoms in different settings and summary review/synthesis 	<ul style="list-style-type: none"> Need to incorporate increases in GUD with HIV infection for high HIV-prevalence areas Disease estimates built upon infection estimates add uncertainty on top of uncertainty
Neonatal herpes	<ul style="list-style-type: none"> First global and regional neonatal herpes estimates published in 2017 	<ul style="list-style-type: none"> Update models as new/better data become available 	<ul style="list-style-type: none"> Better primary data on neonatal herpes incidence is critical, especially in LMICs 	<ul style="list-style-type: none"> Current estimates a good starting point to inform business case, but better data needed

	<ul style="list-style-type: none"> GBD study does not currently include neonatal herpes as HSV outcome 		<ul style="list-style-type: none"> Explore surveillance/research networks evaluating neonatal deaths, infections and other outcomes to include HSV testing Better data on proportion of pregnant women shedding HSV during labor and transmission risks in different settings Better data on proportion of pregnant women acquiring new HSV infections in late pregnancy 	<ul style="list-style-type: none"> Better neonatal herpes numbers critical factor in determining DALYs for HSV Disease estimates built upon infection estimates add uncertainty on top of uncertainty
HSV-related HIV infection	<ul style="list-style-type: none"> Several modelling studies have evaluated population attributable fraction (PAF) of HSV-2 to HIV; good start Published studies limited to particular regions/settings GBD study does not currently include HSV as risk factor for HIV 	<ul style="list-style-type: none"> More comprehensive, updated models of new HIV infections attributable to HSV-2 infections Global and regional estimates, considering geographical areas with different epidemiologic scenarios Work toward including HSV as risk factor for HIV in GBD study 	<ul style="list-style-type: none"> Updated review and meta-analysis of the association between HSV and HIV infection Better understanding of the risk of HIV associated with genital HSV-1 infection 	<ul style="list-style-type: none"> Epidemiologic scenarios: at least high HSV/high HIV prevalence, high HSV/low HIV prevalence, low HSV/low HIV prevalence Consider early vs mature HIV epidemics and where there are existing data Add in alternative interventions (ARVs, PrEP, etc) to models Published models may not yet be sufficient for business case
HSV-1 related oral ulcer disease	<ul style="list-style-type: none"> No identified comprehensive modelled estimates 	<ul style="list-style-type: none"> Estimates of global and regional HSV-related oral ulcerative disease needed, even if roughly apply proportions with symptomatic and recurrent disease 	<ul style="list-style-type: none"> Systematic review of the occurrence of oral HSV disease Review of the natural history of oral HSV-1, including the proportion of oral HSV infections that are ever symptomatic and recurrent Evaluation of administrative or claims data on oral HSV-1 evaluations or treatment 	<ul style="list-style-type: none"> Consider dentistry/oral medicine literature and collaborators
Other HSV-related outcomes: Encephalitis, keratitis, meningo-encephalitis, disseminated disease, etc.	<ul style="list-style-type: none"> No identified comprehensive modelled estimates that include range of HSV-related outcomes 	<ul style="list-style-type: none"> Summary of best estimates of the occurrence of each of the more rare outcomes, especially encephalitis and keratitis 	<ul style="list-style-type: none"> Literature reviews focusing on the individual HSV-related outcomes 	<ul style="list-style-type: none"> Consider the importance of immunocompromised populations
Psychosocial impact,	<ul style="list-style-type: none"> Psychosocial impact (including 	<ul style="list-style-type: none"> Need estimates of quality of life 	<ul style="list-style-type: none"> Expand on pilot studies showing 	<ul style="list-style-type: none"> Most tools focus on symptoms

quality of life, quality-adjusted life years (QALYs)	<p>stigma, effect on relationships) hard to assess for HSV</p> <ul style="list-style-type: none"> No identified cost-effectiveness studies using QALYs, but several good tools exist to estimate impact of HSV on quality of life Several estimates of impact of neonatal herpes on quality of life in HICs 	<p>impact of HSV in adults, including in LMICs, e.g., lifetime QALY loss per case of adult HSV</p> <ul style="list-style-type: none"> Updated estimates of quality of life impact of neonatal herpes, including LMICs where possible 	<p>that commonly used quality of life metrics yield results consistent with the Recurrent Genital Herpes Quality of Life (RGHQoL) scale</p> <ul style="list-style-type: none"> Clarify and get consensus on definitions to derive QALY estimates using existing tools Get quality of life data using RGHQoL and other tools in LMICs 	<p>and daily functioning; more difficult to capture effects of stigma, effect on current and future relationships, etc.</p>
Years lived with disability (YLDs) and disability-adjusted life years (DALYs)	<ul style="list-style-type: none"> YLDs/DALYs for HSV included in GBD 2013; however, YLD estimates do not currently include neonatal herpes and HSV-related HIV infection No other identified models include YLDs/DALYs as outcomes 	<ul style="list-style-type: none"> Work toward adding HSV-related HIV infection and neonatal herpes in YLD/DALY calculations for HSV in GBD 	<ul style="list-style-type: none"> Add genital herpes to GBD Disability Weights Survey Cross-sectional surveys of those with initial/recurrent infection with SF-12 or WHODAS-2 another option to quantify health loss Clarify methods to determine DALYs across groups 	<ul style="list-style-type: none"> Better neonatal herpes numbers critical factor in determining DALYs for HSV

Table 2: Key gaps to be addressed related to modelling of HSV costs

Costs:	Summary of existing or planned models/estimates	Major gaps/ new modelling efforts needed	Key new data needs	Important considerations
HSV-2 infection	<ul style="list-style-type: none"> • A few national estimates of direct annual costs of diagnosing and treating HSV-2 exist for US • Lifetime cost-per-case estimate in US (for diagnosis/treatment) • One estimate of indirect costs • Main estimates do not include costs of neonatal herpes nor HSV-associated HIV and use older cost data (2000 or before) • No aggregate annual cost nor lifetime cost-per-case estimates found for other countries • Many itemized cost components available in HICs, e.g., for HSV testing, counseling, suppressive therapy, clinician visits 	<ul style="list-style-type: none"> • Estimates of costs, both aggregate annual and lifetime cost-per-case, outside the US, especially LMICs • Cost estimates that incorporate neonatal herpes and HSV-associated HIV infection • Updated cost estimates, using current data on HSV testing, antiviral use, other measures 	<ul style="list-style-type: none"> • Review of HSV care and treatment costs, especially in LMICs • Review of care-seeking, health care utilization, testing practices in different settings for HSV disease, especially in LMICs • Utilization rates of episodic and chronic suppressive therapy for HSV in HICs and LMICs 	<ul style="list-style-type: none"> • Use of multiple data sources, including administrative or claims data, where possible • Explore validated healthcare costs in LMICs for similar conditions • Consider time frame, horizon of analysis • For LMICs, consider costs that would be incurred if national recommendations followed; treatment may not be used because too expensive, but vaccine may have relatively lower costs to provide standard of care
HSV-1 infection	<ul style="list-style-type: none"> • No identified comprehensive cost estimates 	<ul style="list-style-type: none"> • Estimates of costs, aggregate annual and lifetime cost-per-case, in both HICs and LMICs • Incorporation of current data on utilization of care and treatment for HSV-1-related outcomes 	<ul style="list-style-type: none"> • Better information on HSV-1 disease occurrence and natural history (see Table 1 above) • Evaluation of administrative or claims data on oral HSV-1 evaluations and treatment • Review oral HSV treatment and administration costs (if different than genital HSV costs above, e.g., topical treatment or over the counter medications) 	<ul style="list-style-type: none"> • Consider dentistry/oral medicine literature and collaborators
Neonatal herpes	<ul style="list-style-type: none"> • Estimates of lifetime cost per case of neonatal herpes available for US, but not other countries • Estimates vary substantially based on whether long-term 	<ul style="list-style-type: none"> • Aggregate annual and lifetime HSV cost-per-case estimates that include neonatal herpes costs • Lifetime cost-per-case estimates for neonatal herpes outside the US, especially LMICs 	<ul style="list-style-type: none"> • Better data on risks of neonatal HSV transmission and neonatal herpes incidence in LMICs (see Table 1) • Neonatal HSV testing, treatment methods and rates, and other 	<ul style="list-style-type: none"> • Consider costs of neonatal herpes prevention, including serological testing, suppressive therapy, and Caesarean sections • Use of multiple data sources, including administrative or

	<p>disability costs included</p> <ul style="list-style-type: none"> • Neonatal herpes costs not systematically included in US aggregate annual cost estimates • Several studies of cost-effectiveness of HSV screening and suppressive therapy in pregnant women • Many itemized cost components available in HICs, including acute neonatal herpes hospitalization costs 	<ul style="list-style-type: none"> • Update neonatal herpes cost estimates using current data on costs, clinical practice, and long-term disability, as well as indirect costs 	<p>healthcare costs in different settings</p> <ul style="list-style-type: none"> • Better data on long-term outcomes and associated disability costs in all settings 	<p>claims data, where possible</p>
HSV-related HIV infection	<ul style="list-style-type: none"> • No specific models of costs pertaining to HSV-related HIV infection, but several models of estimated HIV costs 	<ul style="list-style-type: none"> • Aggregate annual and lifetime HSV cost-per-case estimates that include HSV-related HIV infection costs 	<ul style="list-style-type: none"> • Updated models of the attributable fraction of HIV due to HSV infection (see Table 1) • Review of existing cost estimates for HIV infection 	<ul style="list-style-type: none"> • Consider effect of HSV-HIV co-infection on the natural histories of each, and associated costs (e.g., worsening genital ulcer disease, clinical progression of HIV, etc.)

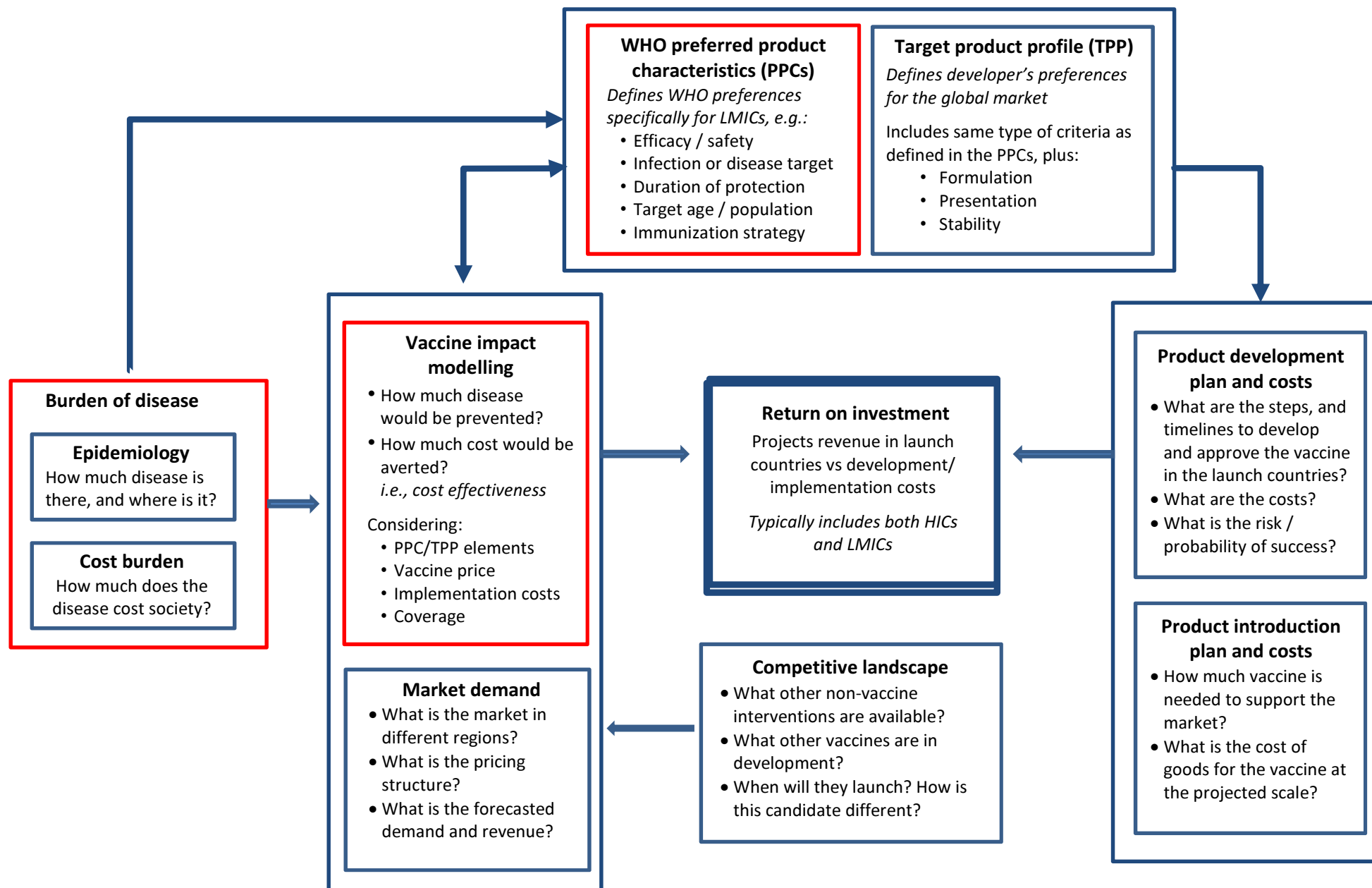


Figure 1. Elements of the comprehensive business case. Elements which are informed by modelling and discussed in this paper are outlined in red. The characteristics as defined within the TPP may be the same as those within the PPCs if the vaccine is predominantly targeted to low- and middle-income countries (LMICs). However, TPPs typically also consider high-income country (HIC) markets, so characteristics defined within a TPP may differ from those within WHO PPCs.

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